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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/109,119 | 06/30/98 | BOLDT | B GTIBEN.001 |

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| EXAMINER | |
|---|---|
| GOLDBERG, J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1655 | 12 |

**DATE MAILED:** 12/28/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

PTO-90C (Rev. 2/95)

1- File Copy

| Office Action Summary | Application No. 09/109,119 | Applicant(s) BOLDT ET AL. | |
|---|---|---|---|
| | Examiner Jeanine A Enewold Goldberg | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

### *Continued Prosecution Application*

1. The request filed on November 30, 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/109,119 is acceptable and a CPA has been established. An action on the CPA follows.

2. This action is in response to the papers filed November 30, 2000. Currently, claims 1-20 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection necessitated by amendment.

### *Drawings*

5. The drawings are not objected to by the draftsman (see PTO 948).

### *Sequence Rules*

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Specifically, the specification contains nucleic acid sequences which are larger than 10 nucleotides and which have not been identified by a SEQ ID NO. i.e. pages 17 and 20.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-16 are indefinite over the recitation "near". The term "near" in claim 1 and 13 is a relative term which renders the claim indefinite. The term "near" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

B) Claims 1-12 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for testing genomic DNA for conditions but the final process step is determining a condition based on a result selected from the group consisting of detection of amplified polynucleotide strands and no-detection of polynucleotide strands. Therefore the claims are unclear since the final process step does not provide a complete set of steps such that the preamble is accomplished. The final process step is unclear how to determine a condition, since the final process step does not provide how the condition is determined. The final process step only provides additional means for determining a condition because no relationship between "a result" and a "condition" is provided.

C) Claims 13-16 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for detecting a mismatch base in a diagnostic section of genomic DNA but the final process step is determining a condition based on a result selected from the group consisting of detection of amplified polynucleotide strands and no-detection of polynucleotide strands. Therefore the claims are unclear whether the method is a method for detecting a mismatch or a method for determining a condition.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 1, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al. (Nucleic Acids Research, Vol. 17, No. 7, pg. 2503-2516, 1989).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA for a condition by making a solution comprising genomic DNA, adding a primer which hybridizes to a targeted section of the genomic DNA, wherein a base at or near the primer 3' end may not hybridize to the genomic DNA, mixing DNA polymerase

into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, detecting the amplified polynucleotide and finally determining a condition. Specifically, Newton teaches a method to permit analysis of any known mutation in genomic DNA. Newton teaches oligonucleotides with a mismatched 3' residue will not function as primers in the PCR under appropriate conditions. Newton makes a sample of genomic DNA by isolation from blood cells (pg. 2505, para 2)(limitations of Claim 1a, 13a). Newton teaches primers which were used for allele characterization by PCR which have a mismatch at the 3' end and primers which do not have a mismatch at the 3' end (pg. 2505)(limitations of Claim 1b, 13b). Newton mixes the genomic DNA, the amplification primer and Taq DNA polymerase for amplification (pg. 2506)(limitations of Claim 1c,d and 13c, d). The polynucleotides were captured on agarose gel electrophoresis for detection (pg. 2507)(limitations of Claims 1efg and 13efg). Thus, Newton has determined the homozygous normal with respect to the AAT gene S allele or heterozygous S. Newton teaches that ARMS is a system allowing the direct analysis of any locus of interest and thus generally applicable to any inherited disease provided sufficient sequence data is available (pg. 2512).

9. Claims 1-2, 13, are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al (US Pat. 5,525,494, June 1996).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA for a condition by making a solution comprising genomic DNA, adding a primer which

hybridizes to a targeted section of the genomic DNA, wherein a base at or near the primer 3' end may not hybridize to the genomic DNA, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, detecting the amplified polynucleotide and finally determining a condition. Specifically, Newton teaches ARMS uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a single solid phase (col. 4, lines 55-60). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60). Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7). ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). The extension is analyzed on agarose gel and by solid phase capture and detection (col. 27)(limitations of Claim 2). An oligonucleotide conjugated to alkaline phosphatase is used for detection and for "clear diagnosis that the DNA is from a homozygous S variant of alpha-1 antitrypsin (col. 28)(limitations of Claim 6, 8, 9, 10). Following hybridization, the wells were washed using 2xSSC (col. 24, lines 25-38). Finally, a color development solution comprising alkaline phosphatase and BCIP was added to the solution for visualization (col. 34).

10. Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Urdea (US Pat. 5,200,314, April 1993).

Urdea teaches a kit which comprises a probe, a support, primers specific for an analyte polynucleotide, a labeled probe, DNA polymerase, a denaturation reagent for denaturing the analyte (col. 11-12). Thus, Urdea has taught every limitation of the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 3-12, 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (US Pat. 5,525,494, June 1996) in view of Monforte et al. (US Pat. 5,700,642, December 1997).

Newton et al. (herein referred to as Newton) teaches a method for testing genomic DNA for a condition by making a solution comprising genomic DNA, adding a primer which hybridizes to a targeted section of the genomic DNA, wherein a base at or near the primer 3' end may not hybridize to the genomic DNA, mixing DNA polymerase into the solution, amplifying the genomic DNA if the base at the 3' end of the primer hybridizes, capturing the amplified polynucleotide strand, detecting the amplified polynucleotide and finally determining a condition. Specifically, Newton teaches ARMS

uses primers that allow amplification in an allele specific manner such that amplification is inhibited when the 3' terminal base of the primer is mismatched (col. 4, lines 45-50). ARMS may be used and captured on a single solid phase (col. 4, lines 55-60). Newton teaches that the capture on solid phases is particularly useful in respect of dipstick type assay formats (col. 5, lines 14-15). As provided in Example 5, the specific capture and detection of amplification products based on the S locus of the alpha-1 antitrypsin gene (col. 24, lines 56-60). Oligonucleotides are immobilized to microtitre dishes (col. 26, lines 55-65)(limitations of Claim 7). ARMS analysis is performed using DNA, ARMS primer, and Taq polymerase (col. 27, lines 15-25)(limitations of Claims 1 and 13). The extension is analyzed on agarose gel and by solid phase capture and detection (col. 27)(limitations of Claim 2). An oligonucleotide conjugated to alkaline phosphatase is used for detection and for "clear diagnosis that the DNA is from a homozygous S variant of alpha-1 antitrypsin (col. 28)(limitations of Claim 6, 8, 9, 10). Following hybridization, the wells were washed using 2xSSC (col. 24, lines 25-38). Finally, a color development solution comprising alkaline phosphatase and BCIP was added to the solution for visualization (col. 34).

Newton does not specifically teach denaturing the amplified polynucleotides to form single-stranded polynucleotides prior to hybridization on a solid support.

However, Monforte teaches that primer extension products are routinely denatured from the target, using hear or chemical denaturant. Monforte also teaches "coupling of an oligonucleotide to a solid support may be carried out through a variety of immobilization attachment functional groups" (col. 17, lines 39-45). This includes

biotinylated oligonucleotides which is the immobilized by attachment to a streptavidin-coated support (col. 19, lines 54-66).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Newton for ARMS primer extension on a solid support with the teachings of Monforte that denaturing the extension product is routine in the art prior to subsequent hybridization to a solid support. The skilled artisan would have been motivated to have denatured the primer extension product of Newton with either chemical or heat denaturation methods for the expected benefit of obtaining suitable nucleic acid for further hybridization analysis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the solid support attachment method of Newton with the equivalent as taught by Monforte. The skilled artisan would have recognized by the extensive teachings of Monforte that oligonucleotides may be linked to solid supports using numerous means. The utilization of a streptavidin/biotin was one equivalent means for attaching oligonucleotides to a solid support.

12. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (US Pat. 5,525,494, June 1996) in view of Monforte et al. (US Pat. 5,700,642, December 1997) as applied to claims 3-12, 14-16 above, and further in view of Stratagene (Catalog 1988).

Neither Newton nor Monforte specifically teach packaging all of the necessary reagents into a kit.

However, Stratagene teaches reagent kits offer scientists good return on investment since only the quantities actually needed for the assay are premixed and tested. Stratagene teaches kits save time and money because the kits already come prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Newton in view of Monforte with the teachings of Stratagene to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, solid support, chemicals for denaturing and other reagents of Newton and Monforte into a kit, as taught by Stratagene for the express purpose of saving time and money.

***Conclusion***

**13. No claims allowable over the art.**

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Southern et al. (US Pat. 6,150,095, November 2000) teaches a method of detection of point mutation by hybridization to ASOs and chain extension. Southern teaches tethering oligonucleotides to a solid support followed by determination of primer extension.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
December 22, 2000

W. Gary Jones
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